UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/307,223	05/07/1999	JUDITH A. VARNER	6627-PA11	4575

7590 10/14/2003

Kamrin T. Macknight
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, CA 94105

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	28

DATE MAILED: 10/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/307,223	Varner et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 26, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *121-157* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *121-157* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed August 26, 2003 (Paper No. 27) in response to the Office Action of February 26, 2003 (Paper No. 24) is acknowledged and has been entered. Previously pending claims 1-120 have been canceled and new claims 124-157 have been added. Claims 121-157 are currently being examined. It is noted that the limitations of claim 141 drawn to pathologies other than carcinoma and sarcoma have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claims 121-123 remain rejected under 35 USC 112, first paragraph and newly added claims 124-157 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 24, Section 13, page 8.

Applicant argues that support for the language "antagonist induces endothelial cell apoptosis is found on page 16, lines 25-28 wherein the specification teaches that alpha 5 beta 1 antagonists also induce apoptosis of growth factor stimulated endothelial cells.....". The argument has been considered but has not been found persuasive because the claims as written do not recite the phrase "growth factor stimulated". The claims as written broaden the scope of the invention as originally disclosed in the invention. Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. Claims 152-157 are rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in Paper No. 24, Section 5, pages 3-4, Paper No. 17, Section 5, page 3, Paper No. 15, Section 10, page 16 drawn to the previously pending claims.

Applicant argues that the specification fully describes this amended claim language and points to page 23, lines 5-14 wherein the specification teaches that "as discussed for anti-alpha 5 beta 1 antibodies, a peptide that specifically binds alpha 5 beta 1 can be useful in a method of the invention where the antibody binds to alpha 5 beta 1 with at least a two-fold greater.....". The argument has been considered but has not been found persuasive because the fold greater binding is drawn not to the peptide but to the antibody. Applicant appears to suggest ("[sic? Should be peptide?]" that an error was made in the writing of the specification. The intentions of the writer of the specification are not relevant here. What is relevant is the specification as originally filed and as originally filed, the "fold" information is drawn not to the peptide but to an antibody. Applicant's arguments have not been found persuasive.

6. Claim 151 is rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of "a dose of 0:0001" has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for a dose of "0.0001" in claim 75 as originally filed. However, there is no support for the newly added limitation, which appears to be a typographical error. Amendment of claim 151 to

delete the colon and substitute a period after the first "0" would obviate the instant rejection.

Claim Rejections - 35 USC § 102

7. Claims 121-131, 135-144, 147, 149-157 are rejected under 35 USC 102(e) essentially for the reasons previously set forth in Paper No. 24, Sections 8-10, pages 5-7, Paper No. 17, Sections 8-10, pages 7-12, Paper No. 15 Sections 5-7, pages 3-9 and in Paper No. 9, Sections 8, pages 5-8 drawn to the previously pending claims.

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue, in an individual, reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising contacting alpha 5 beta 1 integrin in the tissue with an antagonist that induces endothelial cell apoptosis and that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue (claims 121-123) wherein the ligand is fibronectin (claim 124) the tissue comprises ocular tissue from retina, macula or cornea (claims 125-126), wherein the tissue comprises a neoplasm (claim 127 and 136), wherein the neoplasm is malignant (claims 128 and 137), wherein the neoplasm is a metastatic malignant neoplasm (claims 129 and 138), wherein the neoplasm is a carcinoma (claims 130 and 139) wherein the antagonist comprises a peptide (claim 131), wherein the individual is a human (claims 135 and 142), wherein the carcinoma is selected from the group including breast carcinoma, colon carcinoma, ovarian carcinoma and pancreatic carcinoma (claim 140) wherein the malignant neoplasm is a sarcoma (claim 141), wherein the antagonist is administered iv (claim 143), administered orally (claim 144), wherein the

pathological conditions are selected from the group including diabetic retinopathy and macular degeneration by neovascularization (claims 147), wherein the antagonist is administered intravenously (claim 149), wherein the antagonist is administered intravenously (claim 150), wherein the antagonist is administered at a dose of 0.0001 to 100 mg/kg body weight (claim 151). Wherein the antagonist is a peptide and wherein the binding of said peptide is at least two-fold, five-fold, ten-fold greater specificity than the binding of said peptide to an integrin other than alpha 5 beta 1, wherein the other integrin is alpha V beta 3 integrin (claims 152-157).

As previously set forth in Paper No. 9, it is noted that the term "peptide" as defined by the specification is broadly used to include oligomers and polymers of amino acids that are linked by a peptide bond. The specification further states that the term peptides includes molecules commonly referred to as peptides which generally contain two to about fifty amino acids. It is assumed, for purposes of examination, this definition is not limiting.

As previously noted, WO95/14714 specifically teaches that the only known ligand for alpha 5 beta 1 integrin is fibronectin (page 2, lines 3-4).

US Patent No. 5,922,676 teaches a method of inhibiting angiogenesis and treating pathologies with angioproliferative components comprising administering superfibronectin (sFN) to a subject. Superfibronectin is a multimer of fibronectin (col 4, lines 11-15). The pathologies to be treated with the method include cancer, ocular neovascularization, diabetic retinopathy and in particular the patent provides methods for inhibiting metastasis of osteosarcoma and colon, breast or ovarian

carcinoma (col 2, lines 35-48). The effective amount to be administered can be about 0.1 micrograms/kg to about 100 mg/kg body weight (col 8 (lines 55-60). US Patent No. 5,922,676 specifically teaches that sFN is a form of fibronectin (col 1, lines 55-60) and teaches that the term "subject" as used in the patent means a vertebrate, preferably a mammal and in particular, a human (col 5, lines 63-64). Further, the term "administering" comprises any method of administration known to one skilled in the art including intravenously orally and topically (col 9, lines 20-40). Although the reference does not specifically state that the method comprises contacting alpha 5 beta 1 integrin with an antagonist that interferes with specific binding of the alpha 5 beta 1 integrin to its ligand or that the ligand is fibronectin or that the antagonist does not substantially interfere with the binding of a ligand to an integrin other than alpha 5 beta 1, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Further, as previously set forth in Paper No. 15, US Patent No. 5,922,676 teaches as set forth previously and above and further teaches that the administration

of sFN causes regression of established primary tumors *in vivo* (see Example VII). WO95/14714 further teaches that the known alpha and beta subunits of integrins associate in various combinations to form at least twenty receptors with different ligand specificities (p. 1, lines 10-15) and that fibronectin is a ligand that is specific for alpha 5 beta 1 receptor in that alpha 5 beta 1 is the fibronectin receptor (page 2, lines 3-5) and specifically teaches that a molecule "selectively binds to an integrin if it binds with a 10-fold or higher affinity to that integrin as compared to another integrin and that a peptide is "specific for" an integrin if it binds to that integrin with a 100-fold higher affinity as compared to another (p. 12, lines 18-25). Given that alpha 5 beta 1 is the fibronectin receptor, it would be expected that fibronectin not only selectively binds to alpha 5 beta 1 but also that it is specific for alpha 5 beta 1 and that thus all of the limitations of the claims are met. Although the reference does not specifically state that the antagonist of the method binds alpha 5 beta 1 integrin at least two-fold, five-ten fold, ten fold greater than any other integrin, alpha V beta 3, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Further, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an antagonist, which binds alpha 5 beta 1 integrin (which is expected to interfere with the specific binding of endogenous ligand to alpha 5 beta 1 integrin for the reasons of record) to the same population, that is to a tissue/individual, with a neoplasm, carcinoma, metastasis, thus the claimed method is anticipated because the method will inherently lead to reducing or inhibiting angiogenesis. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Further, as previously set forth in Paper No. 15, US Patent No. 5,922,676 as evidenced by WO95/14714 teach as set forth above. Pytela specifically teaches that alpha 5 beta 1 is selective for fibronectin. WO95/14714 further teaches that the known alpha and beta subunits of integrins associate in various combinations to form at least twenty receptors with different ligand specificities (p. 1, lines 10-15) and that fibronectin is a ligand that is specific for alpha 5 beta 1 receptor in that alpha 5 beta 1 is the fibronectin receptor (page 2, lines 3-5) and specifically teaches that a molecule that "selectively binds to an integrin if it binds with a 10-fold or higher affinity to that integrin as compared to another integrin and that a peptide is "specific for" an integrin if it binds to that integrin with a 100-fold higher affinity as compared to another (p. 12, lines 18-25). Given that alpha 5 beta 1 is the fibronectin receptor, it would be expected that fibronectin not only selectively binds to alpha 5 beta 1 but also that it is specific for alpha 5 beta 1 and that thus all of the limitations of the claims are met. Although the reference does not specifically state that the antagonist of the method binds alpha 5 beta 1 integrin at least two-fold, five-

ten fold, ten fold greater than any other integrin, alpha V beta 3, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Finally as drawn to the limitation wherein said "antagonist induces endothelial cell apoptosis", although the prior art reference does not specifically state that antagonist induces endothelial cell apoptosis, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

In addition, again as drawn to the limitation wherein said "antagonist induces endothelial cell apoptosis", the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an antagonist, which binds alpha 5 beta 1 integrin to the same population, that is to a tissue/individual, with a neoplasm, carcinoma, metastasis, thus the claimed method is anticipated because the method will inherently lead to the induction of endothelial cell apoptosis. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claim Rejections - 35 USC § 103

8. Claims 121, 131-134, 145-146, 148 are rejected under 35 USC 103 as being unpatentable over US Patent No. 5,922,676, of record, in view of WO95/14714 of record, Thorpe of record and further in view of Guo et al (Cancer Research, 1997, 57:1735-1742) and Scott et al (J. Invest. Derm., 1997, 108:147-153).

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue comprising contacting alpha 5 beta 1 integrin in the tissue with an antagonist that induces endothelial cell apoptosis and that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue (claim 121), whereby reducing or inhibiting angiogenesis in the tissue, wherein the antagonist is a peptide, and comprises SEQ ID NO:1 (claims 131-132),wherein the antagonist is linked to a cytotoxin, a chemotherapeutic drug (claims 133-134), wherein the antagonist is administered into a neoplasm (claim 145), wherein the pathological condition is associated with the eye (claim 146), wherein the antagonist is administered in the form of eye drops (claim 148).

US Patent No. 5,922,676 teaches as set forth above and further teaches that, SEQ ID NO:18 of US Patent No. 5,922,676 is an alpha 5 beta 1 directed peptide which inhibits tumor metastasis. It is noted that SEQ ID NO: 18 has 100% identity to SEQ ID NO:1. The reference does not teach that the peptide is SEQ ID NO:1, the peptide linked to a cytotoxin, wherein the cytotoxin is a cancer chemotherapeutic drug, wherein the antagonist is administered into a neoplasm, wherein the antagonist is administered by eye drops, wherein the antagonist is administered into the neoplasm..

WO95/14714 teaches as set forth above and further specifically teaches a therapeutic method useful for inhibiting metastasis of tumor cells expressing alpha 5 beta 1 integrin comprising administering a peptide wherein the peptide selectively binds alpha 5 beta 1 integrin ((p. 4, lines 28-32) whose ligand is fibronectin (page 2, lines 3-4), wherein SEQ ID NO:6 (which comprises claimed SEQ ID NO:1) specifically inhibits cell attachment to fibronectin (figures 5 and 6) and specifically teaches the inhibition of tumor metastasis with peptides of the invention directed toward tumors expressing the alpha 5 beta 1 integrin (para bridging pages 20 and 21), which include SEQ ID NO:6 and SEQ ID NO:12 (which is identical to the claimed SEQ ID NO:1). The reference further teaches that the amounts of peptide to be administered can be determined by the assay shown in figure 1, wherein it is demonstrated that dosages of from 1-1000 micrograms are appropriate for SEQ ID NO:6 (page 21, lines 14-22 and Figure 1).

Thorpe teaches procedures for conjugating antagonists that target tumor cells to a variety of different moieties, including cytotoxins (see entire article). and

teaches that by carrying the cytotoxic antagonist specifically to the tumor, the rest of the body should encounter relatively low levels of drug and so be spared from harm (p. 475, Introduction).

Guo et al specifically teach that fibronectin matrix provides strong survival-promoting signals and suppresses apoptosis in endothelial cells (see abstract)

Scott et al teaches that fibronectin suppresses apoptosis in human melanocytes. Scott et al further teach that prevention of attachment to fibronectin matrix is a potent inducer of apoptosis. A role for the beta1-integrin family in mediating cell survival signals was shown by the ability to beta1-blocking antibodies to enhance apoptosis in melanocytes attached to fibronectin.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute SEQ ID NO:6 or SEQ ID NO:12 of WO95/14714 for the sFN of US Patent No. 5,922,676 in the methods of US Patent No. 5,922,676 because both antagonists bind/target alpha 5 beta 1 integrin and because US Patent No. 5,922,676 specifically teaches that SEQ ID NO 18 inhibits cancer cell metastasis in a manner substantially equivalent to that of sFN and WO95/14714 specifically teaches a method useful for inhibiting metastasis using the recited peptides. One of ordinary skill in the art would have been motivated to substitute SEQ ID NO:6 or SEQ ID NO:12 of WO95/14714 for the sFN of US Patent No. 5,922,676 in the methods of US Patent No. 5,922,676 because WO95/14714 specifically teaches the inhibition of tumor metastasis with peptides of the invention directed toward tumors expressing the alpha 5 beta 1 integrin.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that the prior art antagonists would also induce endothelial cell apoptosis because both Guo et al and Scott et al teach that it was known in the art that fibronectin suppresses apoptosis in cell types, including endothelial cells and because Scott et al specifically demonstrate that beta1-blocking antibodies, which bind to the alpha 5 beta 1 integrin, enhance apoptosis in cells attached to fibronectin. Given that fibronectin was known to suppress apoptosis and that beta1 blocking antibodies enhance apoptosis, apparently by inhibiting the suppression, it would be expected that fibronectin antagonists including the antagonists of WO95/14714 would antagonize the apoptosis suppression of fibronectin.

It would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to administer the antagonist for treatment of ocular pathology by administration of eye drops because US Patent No. 5,922,676 specifically teaches the topical administration of the antagonist of the invention.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to link the antagonists of either US Patent No. 5,922,676 or WO95/14714 to a cytotoxin using the method taught by Thorpe. One of ordinary skill in the art would have been motivated to produce the claimed cytotoxin-linked antagonists in view of the teachings that such cytotoxin-linked antagonists are useful for diagnosis of refractory tumors and the general knowledge that antibodies or peptides can be successfully targeted to tumor cells. One would further have been motivated to link a chemotherapeutic cytotoxin to the peptide

antagonist in order to target a chemotherapeutic to the tumor site. Finally, it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to inject the antagonists directly into the tumor in the methods of either US Patent No. 5,922,676 or WO95/14714 in order reduce diffusion and non-specific sequestration of the antagonists.

9. All other objections and rejections recited in Paper No. 24 are hereby withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 10, 2003